



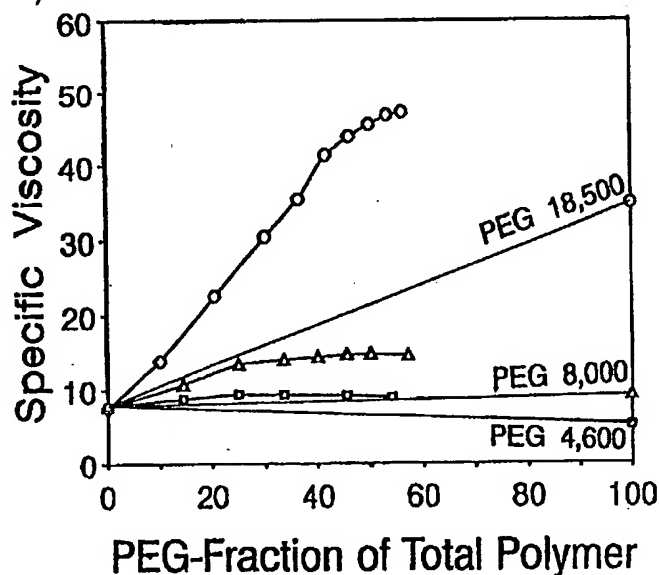
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(54) Title: IN SITU GEL-FORMING DELIVERY VEHICLE FOR BIO-AFFECTING SUBSTANCES, AND METHOD OF USE



## (57) Abstract

An interpolymer complex of a polyacid and a water-soluble, non-ionic polymer, preferably polymethacrylic acid and polyethyleneglycol, which forms a stable, insoluble complex in water at acidic pH, and which is converted to an extrudable liquid upon addition of an appropriate amount of a complex solubilizer, preferably ethanol. The resultant complex is particularly useful as an injectable, sustained release delivery vehicle for bio-affecting substances, including therapeutic agents.

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**IN SITU GEL-FORMING DELIVERY VEHICLE  
FOR BIO-AFFECTING SUBSTANCES, AND METHOD OF USE**

**BACKGROUND OF THE INVENTION**

The present invention relates to compositions and methods for sustained delivery of bio-affecting substances and in particular to  
5 injectable pharmaceutical compositions which transform to a slowly erodible gel following introduction into a physiological environment.

Various methods have been proposed for efficient delivery of a therapeutic agent to its site  
10 of action. Early efforts to develop a sustained release drug delivery system were directed toward incorporating therapeutic agents into solid or semi-solid vehicles for application to or implantation under the patient's skin. A number of semi-solid  
15 ointments or gels have been shown to be effective for increasing drug retention times in the case of ophthalmic drug delivery. See, for example, U.S. Patents Nos. 3,700,451, 3,944,427 and 4,100,271.

More recently, attempts have been made to  
20 develop gelling drug delivery systems capable of administration via injection. One such system utilizes a polymeric delivery vehicle that is liquid at room temperature, but forms a semi-solid gel when warmed to body temperature. In U.S. Patent 4,188,373,  
25 for example, a gel-forming drug delivery system is disclosed which utilizes proprietary non-ionic difunctional polyoxyalkylene derivatives of propylene glycol (known as Pluronic® polyols) as the thermally gelling polymer. The desired sol-gel transition  
30 temperature is said to be obtained by appropriate adjustment of the polymer concentration. Specifically, the lower the concentration of polymer, the higher the sol-gel transition temperature; a gel will not form below a critical minimum concentration.

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U.S. Patent 4,474,752 discloses an injectable sustained release drug delivery system, based on proprietary non-ionic tetrafunctional polyoxyalkylene derivatives of ethylenediamine (known  
5 as Tetronic® polyols), which gel at temperatures from about 30°-100°C. The sol-gel transition temperature and rigidity of the gel are said to be capable of modification by changes in polymer concentration combined with the pH and ionic strength of the  
10 solution.

Although effective for increasing drug retention times, these thermally formed gels dissolve relatively rapidly due to their weak gel structure.

U.S. Patent 5,124,151 discloses injectable  
15 compositions for sustained drug delivery utilizing thermo-irreversible gels as delivery vehicles. The compositions comprise mixtures of a polyoxyalkylene polymer and an ionic polysaccharide, and a latent counter-ion, the release of which causes the  
20 polysaccharide to gel. At ambient temperature, the compositions are low viscosity liquids, but upon administration to the patient the counter-ion is released to gel the polysaccharide, which forms a semi-solid gel of high viscosity.

25 Reversibly gelling compositions useful as drug delivery vehicles are the subject of U.S. Patent 5,252,318, which discloses an aqueous composition containing effective concentrations of a stable combination of at least one thermally-sensitive  
30 gelling polymer and at least one pH-sensitive gelling polymer, that can be formulated to undergo a specific sol-gel transition over pre-determined temperature and pH ranges, thus making the compositions useful as drop-instillable aqueous wetting agents and drug  
35 delivery systems. These aqueous compositions are low viscosity liquids at ambient temperature and a pH

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range of 2.5 to 6.5, but are transformed to high viscosity, semi-solid gels when exposed to physiological pH and a temperature of 37°C.

5 U.S. Patent 5,292,516 relates to the use of isotonic, iso-osmotic, pH-balanced thermoreversible gels containing polyoxyalkylene copolymers as vehicles for drug delivery to a body cavity of a mammal.

10 U.S. Patent 5,292,517 is concerned with a sustained-release drug delivery vehicle comprising a liquid solution of poly(methylvinylether/maleic acid) copolymer with a therapeutic or diagnostic agent incorporated therein, which reversibly gels in response to changes in pH. These compositions are said to be useful as dropable or injectable drug  
15 delivery systems for the sustained delivery of pharmaceutical compounds.

Various cross-linked polymer hydrogels have also been proposed for achieving sustained release of various therapeutic agents. Hydrogel-based drug  
20 delivery systems frequently involve surgical implantation in the patient. Furthermore, the cross-linking agents used are often toxic substances, thus requiring that the hydrogel undergo extensive purification. Cross-linked polymer hydrogels are also  
25 relatively difficult to sterilize.

Interpolymer complexes formed between polyacids and water-soluble non-ionic polymers, e.g., polymethylacrylic acid and polyethyleneglycol, as well as their properties, have been the subject of  
30 extensive investigation, the results of which have been widely published. See, for example, E. Bekturov and L. Bimendina, Adv. Polym. Sci., 41: 99-147 (1981), and references cited therein. Potential practical applications of such interpolymer complexes include  
35 films for uses including transparent and electroconductive plates for illuminating and heating

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purposes, battery separators, wearing apparel, wallcoverings, and dialysis and ultrafiltration systems. Hydrogels from these polymer complexes have also been proposed for use as contact lenses, tissue  
5 substitutes and prosthetic devices. Insofar as is known, however, such interpolymer complexes have never been proposed heretofore for use as delivery vehicles for sustained release of bio-affecting substances.

#### SUMMARY OF THE INVENTION

10 The present invention provides improved pharmaceutical compositions capable of sustained release of therapeutic agents and diagnostic agents, wherein the improvement comprises a gel-forming delivery vehicle comprising a solution of at least one  
15 pharmaceutically acceptable polyacid and at least one pharmaceutically acceptable water-soluble, non-ionic polymer, the polyacid and the non-ionic polymer forming a stable, insoluble interpolymer complex in water at acidic pH, in an aqueous solvent including a  
20 pharmaceutically acceptable complex solubilizer, the amount of the complex solubilizer being effective to solubilize such insoluble interpolymer complex.

The interpolymer complex, which is initially a gum-like mass at low pH, is converted to a clear  
25 liquid upon solubilization in the aforementioned solvent. The resultant liquid is readily extruded through the cannula of a conventional hypodermic syringe. When introduced into a physiological environment, e.g., by subcutaneous or intramuscular  
30 injection, the liquid forms a semi-solid gel which erodes slowly over a period of several days.

The gel-forming property of the delivery vehicle of the invention makes it well suited for administration of numerous therapeutic and diagnostic  
35 agents via injection to achieve improved

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not require the use of cross-linking agents, thus eliminating a potentially toxic component from the composition. Furthermore, according to a preferred embodiment of the present invention in which ethanol of appropriate concentration is used as the interpolymer complex solubilizer, sterilization of the delivery vehicle occurs as a matter of course in the process of its preparation.

The gel-forming delivery vehicle described herein has a relatively strong gel structure, thereby providing enhanced duration of the therapeutic or diagnostic agents incorporated therein. Also, because the gel components are readily eliminated from the body due to their low molecular weights, the need for chemical degradation in the body is obviated.

Additional advantages and features of the present invention are set forth in, and will be apparent to those skilled in the art from the detailed description of the invention presented below considered in conjunction with the accompanying drawings.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graphical illustration showing the specific viscosity of the delivery vehicle as a function of the ratio of polyethylene glycol to total polymer concentration for different molecular weights of polyethylene glycol (□ represents polyethylene glycol (PEG) of 4,600 molecular weight (MW); Δ represents PEG of 8,000 MW; O represents PEG of 18,500 MW).

FIG. 2 is a graphical illustration showing the gain (ratio for viscosity change due to complexation) as a function of polyacid to non-ionic polymer ratio for a preferred drug delivery vehicle of the present invention (□ represents PEG of 4,600 MW; Δ

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bioavailability and sustained release of the therapeutic and diagnostic agents. The delivery vehicle of the invention may also be beneficially used, if desired, for microencapsulation of therapeutic or diagnostic agents for parenteral administration or for implantation of wound healing drugs, e.g., after surgery.

The components of the delivery vehicle are water soluble, non-toxic substances that are readily eliminated via the kidneys due to their low molecular weight.

The present invention further provides a method for sustained delivery of a therapeutic agent to a patient. The method involves administering to the patient, preferably by injection, the gel-forming delivery vehicle described immediately above, including an effective amount of a therapeutic or diagnostic agent. The gel-forming delivery vehicle of the invention can be used with a wide range of bio-affecting substances of varying molecular weight, and in particular those substances for which systemic distribution is undesired, such as chemotherapeutic agents or analogous diagnostic agents, which may be injected directly into tumors.

The gel-forming delivery vehicle and its method of use in accordance with the present invention offer several notable advantages over *in situ* gel-forming drug delivery systems and methods of the prior art, particularly those utilizing cross-linked polymer hydrogels. The starting materials for the drug delivery vehicle of this invention are available from various commercial sources and are easily formulated into the desired pharmaceutical composition according to relatively simple procedures. Moreover, the starting materials used to prepare the gel-forming delivery vehicle according to the present invention do



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represents PEG of 8,000 MW; O represents PEG of 18,500 MW).

FIG. 3 is a graphical illustration of the results of a study of solution-gel transformation as a function of temperature and solvent compositions for a preferred drug delivery vehicle of the invention (FR=Formulation range for best syringability).

#### DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, it has now been discovered that certain complex-forming pharmaceutically acceptable macromolecules are capable of functioning as an *in-situ* gelling delivery vehicle for administration of various bio-affecting substances, including therapeutic agents and diagnostic agents, preferably via injection, thereby enabling sustained release of the bio-affecting substance.

As used herein with reference to the several components of the gel-forming delivery vehicle of the invention, the expression "pharmaceutically acceptable" refers to substances which do not adversely affect the activity or efficacy of the bio-affecting substance included in the delivery vehicle and which are not in themselves toxic to the recipient.

The complex-forming macromolecules include pharmaceutically acceptable polyacids and water-soluble, non-ionic polymers that form a stable interpolymer complex in water under acidic conditions. Representative polyacids include polyacrylic acid, polymethacrylic acid, co-polymers of acrylic acid with acrylic acid esters, e.g., ethylacrylate, or with methacrylic acid esters, e.g., ethylmethacrylate and co-polymers of methacrylic acid with acrylic acid esters or with methacrylic acid esters.

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Representative water-soluble, non-ionic polymers that form interpolymer complexes with the aforementioned polyacids include hydrogen bond acceptors from the group of polyether glycols, such as polyethylene glycol or polypropylene glycol, polyvinylpyrrolidone polyoxyalkylene derivatives of ethylene diamine or polyoxyalkylene derivatives of propylene glycol.

The molecular weight of the individual polymeric components of the delivery vehicle of the invention should be less than about 50,000 to allow for elimination of these components by glomerular filtration. Preferably, the polyacid has a weight average molecular weight of from about 4,000 to about 40,000 and the non-ionic polymer has a weight average molecular weight from about 2,000 to about 40,000.

The ratio of polyacid to non-ionic polymer in the delivery vehicle, based on the number of repeat units in each polymer, should generally be in the range of 5:1 to 1:5. Preferably, this ratio should be on the order of 2:1 to 1:2, with a ratio of 1:1 being most preferred.

The polyacid and non-ionic polymer form a stable interpolymer complex having an insoluble gel structure in water at acidic pH, presumably due to a combination of van der Waal forces, hydrogen-bonding and hydrophobic interaction between the polymer chains. It appears that non-ionized carboxyl groups are necessary for cooperative hydrogen-bonding to occur. When acidic conditions are not maintained, the interpolymer complex tends to break down, the reason apparently being that there is inadequate non-ionized carboxyl groups for complexation to occur. Specific complex-forming polyacid-non-ionic polymer pairs have characteristic pH maximums, above which complexation will not occur. For example, breakdown of

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polymethacrylic acid-polyethylene glycol and polyacrylic acid-polyethylene glycol complexes occur if the pH is increased beyond 5.7 and 4.8, respectively. The characteristic pH maximum for any specific polyacid-non-ionic polymer pair can easily be determined by routine experimentation. For the reason already indicated, these characteristic pH maximums depend essentially on the polyacid.

The insoluble gel structure of the interpolymer complex, as noted above, can be eliminated by including in the aqueous solution of the complex an amount of a complex solubilizer that is effective to solubilize the insoluble interpolymer complex. Alcohols have been shown to be effective for this purpose. The ability of alcohols to eliminate the gel structure varies directly according to alkyl chain length; the longer the chain length, the greater the solubilizing effect at a given concentration. The addition of the complex solubilizer yields a clear, viscous liquid which is readily extruded through the cannula of a conventional hypodermic syringe, making the resultant composition useful in injectable, sustained release drug delivery systems.

The amount of alcohol added to the delivery vehicle solution to function as a complex solubilizer in the manner described above is generally in the range of 5-90%, based on the weight of the solution. Particularly good results have been obtained using approximately equal amounts of water and alcohol as the solvent for the delivery vehicle of the invention.

Where sustained release of a therapeutic agent is desired, the pharmaceutical composition of the invention will contain, based on the total weight of the composition, an effective amount of the therapeutic agent, typically from about 0.01 to about 40%, about 4 to about 60% of at least one

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pharmaceutically acceptable polyacid, about 2 to about 30% of at least one pharmaceutically acceptable water-soluble non-ionic polymer capable of forming an interpolymer complex under the above-stated conditions, about 5%-50% water and about 5%-75% of a pharmaceutically acceptable alcohol which functions to solubilize the interpolymer complex in the manner described above. Depending on the condition of the patient, the above-stated amounts may be varied to increase or decrease the dosage schedule, as appropriate. As used herein, the term "therapeutic agent" refers to a substance used in treating or ameliorating a disease or a medical condition.

If desired, the delivery vehicle of the invention may also contain a buffering agent and preservative, in addition to the therapeutic or diagnostic agent. Suitable water-soluble buffering agents include alkali metal or alkaline earth metal carbonates, phosphates, bicarbonates, citrates, borates, acetates, succinates and tromethamine (TRIS). These buffering agents may be present in amounts sufficient to maintain the composition at a pH between 1 to 6, and preferably 4 to 5.5. As such, the buffering agent may be as much as 20% by weight of the total composition, the exact amount depending on the chemical nature of the interpolymer complex and the pH value sought to be maintained. Suitable water-soluble preservatives include sodium bisulfite, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric, borate, parabens, benzylalcohol and phenylethanol. These agents may be present, generally, in amounts of about 0.001% to about 5% by weight and, preferably, in the amount of about 0.01 to about 2%.

Virtually any therapeutic agent or diagnostic agent capable of administration using the

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in situ-gelling compositions of the prior art can be administered using the sustained-release delivery vehicle of the present invention. The following drugs can be administered via injection using the delivery vehicle described herein:

- 5 (1) Analgesics such as aspirin, acetaminophen, diflunisal and the like;
- (2) anesthetics such as lidocaine, procaine, benzocaine, xylocaine and the like;
- (3) antiarthritics such as phenylbutazone, indomethacin, sulindac, dexamethasone, ibuprofen, allopurinol, oxyphenbutazone, theophylline,
- 10 (4) antiasthma drugs such as epinephrine, ephedrine, beclomethasone dipropionate, and the like;
- (5) urinary tract disinfectives such as 15 sulfamethoxazole, trimethoprim, nitrofurantoin, norfloxacin and the like;
- (6) anticoagulants such as heparin, bishydroxy coumarin, warfarin and the like;
- 20 (7) anticonvulsants such as diphenylhydantoin, diazepam and the like;
- (8) antidepressants such as amitriptyline, tolbutamide, chlorpropamide and the like;
- 25 (9) antidiabetics such as insulin, imipramine, doxepin and its analogs, tolazamide, acetohexamide, chlorpropamide and the like;
- (10) antineoplastics such as adriamycin, 30 flurouracil, methotrexate, asparaginase and the like;
- (11) antipsychotics such as prochlorperazine, lithium carbonate, lithium citrate, thioridazine, molindone, fluphenazine, trifluoperazine, perphenazine, amitriptyline, 35 triflupromazine and the like;

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(12) antihypertensives such as  
spironolactone, methyldopa, hydralazine, clonidine,  
chlorothiazide, deserpidine, timolol, propranolol,  
metoprolol, prazosin hydrochloride, reserpine and the  
5 like;

(13) muscle relaxants such as  
succinylcholine chloride, danbrolene, cyclobenzaprine,  
methocarbamol, diazepam and the like;

(14) proteins and peptides such as atrial  
10 natriuretic factor, calcitonin-gene related factor,  
leutinizing hormone, releasing hormone, neurotensin,  
vasoactive intestinal peptide, vasopressin,  
cyclosporine, interferon, substance P enkephalins,  
epidermal growth factor, fibronectin, insulin-like  
15 growth factor and mesodermal growth factor;

(15) immunosuppressive agents and anti-  
metabolites, such as methotrexate, cyclophosphamide,  
6-mercaptopurine and azathiopirine; and

(16) oligonucleotides and DNA fragments;  
20 and

(17) various mixtures of the foregoing  
therapeutic agents, e.g., in combination therapy.

Other suitable drugs which can be  
administered using the drug delivery vehicle of the  
25 present invention are anti-bacterial substances, such  
as beta-lactam antibiotics, tetracyclines,  
chloroamphenicol, neomycin, gramicidin, bacitracin,  
sulfonamide, aminoglycoside antibiotics, tobramycin,  
nitrofurazone, nalidixic acid and analogs, the  
30 antimicrobial combination of fludalanine/pentizidone  
and the like; antihistaminics/decongestants, such as  
perilamine, chlorpheniramine, tetrahydrozoline,  
antazoline, and the like; antiinflammatory drugs, such  
as cortisone, hydrocortisone, betamethasone,  
35 dexamethasone, fluocortolone, prednisolone,  
triamcinolone, indomethacin, sulindac and its salts

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and corresponding sulfide, and the like; anti-parasitic compounds, such as ivermectin and the like; anti-viral compounds, such as acyclovir, interferon, and the like; carbonic anhydrase solubilizers, such as acetazolamide, dichlorphenamide, 2-(p-hydroxyphenyl)thio-5-thiophenesulfonamide, 6-hydroxy-2-benzothiazolesulfonamide, 6-pivaloyloxy-2-benzothiazolesulfonamide, and the like.

Representative diagnostic agents that may be incorporated in the drug delivery vehicle of the present invention include contrast agents, dyes and radiotracers.

The foregoing listing of suitable bio-affecting agents is exemplary only and is not intended to limit the scope of the present invention.

The delivery vehicle may also contain co-solvents, suspending agents, viscosity enhancing agents, ionic strength and osmolality regulating agents and various excipients, in addition to the bio-affecting agent, buffering agent and/or preservative, if desired.

Preferably, the therapeutic or diagnostic agent is water-soluble. Of course, some therapeutic or diagnostic agents will show greater solubility in the delivery vehicle than others. Co-solvents may be beneficially used to enhance drug solubility; however, some therapeutic or diagnostic agents may be insoluble. These can often be suspended in the delivery vehicle with the aid of suitable suspending or viscosity enhancing agents. It has been found that incorporating certain polymeric drugs, e.g., proteins or peptides, into the drug delivery vehicle of the invention can result in phase separation. This is a common phenomenon for polymers of different polarity. In order to avoid phase separation, a pharmaceutically acceptable compatibility promoting agent may be

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included in the composition, up to about 50% by weight, to enhance the ability of the components to remain in close association for a prolonged period of time. Glycerin has been found to be a good  
5 compatability promoting agent for enhancing the miscibility of the delivery vehicle with polymeric drugs. Citric acid is advantageously used in conjunction with the glycerin to maintain the pH below the critical value within the gel, rendering it stable  
10 for a longer period of time.

In the case of administration of therapeutic agents, the composition of the invention would contain from about 0.01 to about 40% by weight of the therapeutic agent, as previously noted. Thus, from 1  
15 gm of the composition, which is about 1.0 ml of solution, there would be obtained about 0.1 mg to about 400 mg of therapeutic agent.

The particular drug used in the pharmaceutical composition of this invention is the  
20 type which a patient would require for pharmacological treatment of the condition from which the patient is suffering.

When used to deliver drugs by injection, the composition of the invention will be administered as a  
25 liquid by means of an appropriate syringe equipped with the appropriate delivery tube or needle. As previously noted, although injection is the preferred mode of administration, the delivery vehicle of the invention may also be used for microencapsulation of  
30 therapeutic or diagnostic agents for parenteral administration or for implantation of wound healing drugs, e.g., after surgery.

Although the process by which the delivery vehicle of the invention slowly erodes upon contact  
35 with a physiological environment has not been thoroughly elucidated, it is believed that a delivery



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vehicle-physiological fluid interface is formed at the site of injection, over which the complex solubilizer migrates out, while physiological fluid migrates in, causing immediate formation of the soft, semi-solid gel.

The following examples are provided to describe the invention in further detail. These examples are intended merely to illustrate specific embodiments of the delivery vehicle of the invention and should in no way be construed as limiting the invention.

#### EXAMPLE 1

##### Determination of Specific Viscosity of Delivery Vehicle as a Function of Varying Polymer Ratios

Given the utility discovered for the interpolymer complexes described herein, the interactions between the macromolecules forming the complexes took on considerable interest and, therefore, formulation range concentrations of the polymers were investigated. Specific viscosities of solutions, initially containing a preferred polyacid, polymethacrylic acid (20% by weight) were measured while polyethylene glycol (also 20% by weight) was added in increments and mixed in a viscometer. In three different experiments, polyethylene glycol having molecular weights of 4,600 (Carbowax 4600 NF, Union Carbide Corp., Danbury, CT), 8,000 (Carbowax 8000 NF, Union Carbide, Corp., Danbury, CT) and 18,500 (Polysciences, Inc., Warrington, PA) were used. All the solutions had a solvent content of 60% ethanol. To ensure optimal complex formation, pH was adjusted to a value of 2. An Ubbelohde-type viscometer with a wide capillary was used, and the experiments were carried out at 25°C.

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The specific viscosity in centipoise versus the ratio of polyethylene glycol to total polymer concentration (20% by weight) is shown in Fig. 1. The co-solvent was 60:40 ethanol-water. The curves represent the apparent viscosity of the mixtures,  $\eta_{\text{Mixture}}$ , while the lines show calculated viscosities,  $\eta_{\text{PEG}} + \eta_{\text{PMAA}}$ , as if no complex were formed. For normalization of the data with respect to the calculated viscosity, a parameter gain, was utilized, which was determined according to the following equation.

$$\text{Gain} = \frac{\eta_{\text{Mixture}}}{\eta_{\text{PEG}} + \eta_{\text{PMAA}}}$$

The gain is the ratio for viscosity change due to complexation. An aqueous solution of complex aggregates are known to have a compact globular structure due, in part, to hydrophobic interactions, and for such low concentrations that there are no interactions between the complex aggregates, the gain can assume values much lower than unity. In ethanolic solutions, where the interactions giving rise to globular complex formation are eliminated, the complexes presumably have an expanded fiber structure. The stickiness of these solutions tends to corroborate this assumption. Deviation from spheric structure has a strong effect on the viscosity, and hence, the gain depends on the length of the fibers. A graph plotting gain versus monomer ratio is shown in Fig. 2. For polyethylene glycol having molecular weight of 8,000, the chains have about the same length as those of polymethylacrylic acid having molecular weight of 15,000, and since the gain essentially has reached its maximum at a monomer ratio equal to unity, the rule of one-on-one stoichiometry is upheld. In the case of

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polyethylene glycol having molecular weight of 4,600, two polyethylene glycol chains can fit on each polymethacrylic acid molecule, and ideally the length of the complex aggregates would be the same as with  
5 polyethylene glycol having 8,000 molecular weight, but since a lower gain was observed, it was concluded that the strength of these complexes was weaker. In the case of polyethylene glycol having 18,500 molecular weight, two polymethacrylic chains can fit on each  
10 polyethylene glycol molecule, making the complex aggregates twice as long, and explaining the greater gain observed in this case.

#### EXAMPLE 2

##### Preparation of Gel-Forming Delivery Vehicle

15 A delivery vehicle was prepared utilizing an interpolymer complex composed of polymethacrylic acid and polyethylene glycol. Since the monomer weight for polymethacrylic acid is close to twice that for polyethylene glycol, the rule of one-on-one  
20 stoichiometry requires the weight concentration for polymethylacrylic acid to be twice that for polyethylene glycol. Accordingly, polymethacrylic acid of 15,000 molecular weight, as the sodium salt, and polyethylene glycol of 18,500 molecular weight  
25 (both obtained from Polysciences, Inc.) were mixed in amounts of 10% and 20%, by weight, respectively, in a beaker until a clear solution was obtained and HCl(10M) was added slowly while the mixture was vigorously stirred. The mixture became turbid, but  
30 after approximately 5 minutes it cleared up leaving a gum-like mass. The mass was recovered, weighed, placed in a separate beaker and dissolved in the smallest possible amount of absolute, dehydrated ethanol (McCormick Distilling Co., Inc., Weston, MO).  
35 The water content of the resultant solution was

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determined using a thermogravimetric instrument, Shimadzu TGA-150, and the weight of water was determined to be about one-third the weight of the solution. The yield of interpolymer complex was over 95%.

When the resultant solution was diluted to twice its volume with an ethanol-water (1:1) solvent mixture, the solution was extrudable through a 20 gauge needle. Use of an ethanol concentration above 60% will serve to sterilize the composition.

A solution of the complex in ethanol-water (75:25) solvent was found to be very sticky and yard-long thin threads were easily drawn upon handling. It thus appears that in addition to eliminating the globular structure of the interpolymer complex, the addition of ethanol causes the complex aggregates to assume an expanded, fibrous structure.

### EXAMPLE 3

#### Temperature-Solvent Composition Studies

The solution-gel transformation was studied at different temperatures and solvent compositions in the manner described herein. Ten solutions, each containing 10% by weight of the polymer complex prepared in accordance with the procedure described in Example 2 above, in different water-soluble ethanol solvent compositions were prepared in 20 ml vials with screwcaps. The solution pH was adjusted using HCl or NaOH, as appropriate. Each vial was heated on a water bath to 80°C, and after shaking, allowed to cool. Phase transformations were observed during cooling.

Fig. 3 shows the results of this study. At low ethanol content, an area was identified wherein the gel at the bottom of the vials was unaffected by heating and shaking. At ethanol contents of 18-50%, a region was seen wherein the gel particles were

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dispersed by shaking of the vials, causing turbidity. In an area between 50 and 90% ethanol content, the solutions were clear and a lower consolute temperature was observed at 17°C and 75% ethanol. Finally, above 90% ethanol content, clear solutions could not be obtained. At physiological temperature (37°C), the solution-to-gel transformation occurs between 48% and 18% ethanol content. Variation in pH between 2 and 5 at particular compositions and temperatures did not affect the phase transformation.

## EXAMPLE 4

Release Profiles of Model Substances

Release profiles were generated for two model substances, to evaluate the delivery of therapeutic and diagnostic agents with substantially different molecular weights. The model substances were rhodamine-B, having a molecular weight of 444, and a hydrophilic polymeric substance having a molecular weight of 7,400. The compositions of the delivery vehicle including the model substances are set forth in Table I.

TABLE I

SUBSTANCE	Rhodamine-B		Polymeric substance	
	Overall Composition	Solvent Composition	Overall Composition	Solvent Composition
Water	30.7	47.0	22.1	35.5
Ethanol	35.0	53.0	17.7	28.4
Glycerol <sup>a</sup>	----	----	22.5	36.1
Citric acid <sup>b</sup>	18.0	----	20.5	----
PEG-PMA complex	16.2	----	16.2	----
Model compound	0.1	----	10	----

<sup>a</sup> Product of Sigma Chemical Co., St. Louis, MO

<sup>b</sup> Product of Fisher Scientific Co., Fair Lawn, NJ

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In carrying out this experiment, 1 gm of the delivery vehicle solution was deposited in a cylindrical plastic cap having an approximate volume of 1 ml with an inner diameter of 0.7 cm and a depth of 0.7 cm. The cap was immersed in 200 ml stirred buffer (phosphate buffered saline) with pH maintained at 7.4 during the experiment. Samples were withdrawn at appropriate time intervals until the gel had dissolved. The samples were analyzed in a Shimadzu UV 160U spectrophotometer. Rhodamine B was detected at a wavelength of 555 nm and the polymeric substance at 271.5 nm, where it had an absorption maximum. At the latter wavelength, the polymer component of the delivery vehicle also had some absorption that was measured separately and subtracted from that of the samples.

It was found that while the pH of the aqueous medium in which the delivery vehicle was immersed was maintained at 7.4, the gel eroded slowly with a rate dependent on the availability of buffer ions at the gel-medium interface. Stirring and the addition of NaOH at appropriate intervals maintained the pH and the buffer strength constant at the interface.

The use of rhodamine B, which is an intensely colored substance, allowed observation of any burst effects. No such effects were observed. On the contrary, a skin-like structure appeared on the surface of the gel, delaying the release during the first few hours. Except for some initial swelling, the water-gel area was constant during the experiment. Since apparently all the model substance was released before the gel was dissolved, it appears that the release mechanism was by diffusion.

In the experiment with the polymeric model substance, a higher degree of swelling was observed, estimated to be about 40%. The model substance was released with essentially a constant rate over a period

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of about 3-1/2 days, and it was concluded that the release mechanism was by erosion from the gel surface, which may be explained in part because of the slower diffusion of the higher molecular weight model substance in the gel.

While certain embodiments of the present invention have been described and/or exemplified above, various other embodiments will be apparent to those skilled in the art from the foregoing disclosure. The present invention is, therefore, not limited to the particular embodiments described and/or exemplified, but is capable of considerable variation and modification without departure from the scope of the amended claims.

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## WHAT IS CLAIMED IS:

1. A pharmaceutical composition including a therapeutic agent and a sustained-release delivery vehicle, wherein the improvement comprises a gelable  
5 delivery vehicle comprising a solution of at least one pharmaceutically acceptable polyacid and at least one pharmaceutically acceptable water-soluble, non-ionic polymer, said polyacid and said non-ionic polymer forming a stable insoluble interpolymer complex in water  
10 at acidic pH, in an aqueous solvent including a pharmaceutically acceptable complex solubilizer, the amount of said solubilizer being effective to solubilize said insoluble interpolymer complex.

2. A pharmaceutical composition as claimed  
15 in claim 1, wherein said pharmaceutically acceptable polyacid is selected from the group consisting of polymers of acrylic acid, polymers of methacrylic acid, co-polymers of acrylic acid with an ester of acrylic acid or an ester of methacrylic acid and co-polymers of  
20 methacrylic acid with an ester of acrylic acid or an ester of methacrylic acid, and said pharmaceutically acceptable water-soluble, non-ionic polymer is selected from the group consisting of polyether glycol, polyvinylpyrrolidone, polyoxyalkylene derivatives of  
25 ethylene diamine or polyoxyalkylene derivatives of propylene glycol.

3. A composition as claimed in claim 1, wherein said complex solubilizer is an alcohol.

4. A composition as claimed in claim 1,  
30 wherein the amount of said alcohol in said solution is in the range of 5-90%, based on the weight of said solution.



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5. A composition as claimed in claim 1, wherein the average molecular weight of each of said polyacid and said water-soluble non-ionic polymer is less than about 50,000.

5           6. A composition as claimed in claim 5, wherein the average molecular weight of said polyacid is from about 4,000 to about 40,000.

7. A composition as claimed in claim 5, wherein the average molecular weight of said non-ionic  
10           polymer is from about 2,000 to about 40,000.

8. A composition as claimed in claim 1, wherein the ratio of polyacid to non-ionic polymer, based on the number of repeat units in each said polymer, is in the range of 5:1 to 1:5.

15           9. A composition as claimed in claim 8, wherein said ratio of polyacid to non-ionic polymer is about 1:1.

10. A composition as claimed in claim 10, wherein said solution optionally includes up to about  
20           50% by weight of a pharmaceutically acceptable compatability promoting agent which renders said therapeutic agent and said delivery vehicle compatible.

11. A composition as claimed in claim 10, wherein said compatability promoting agent comprises  
25           glycerin.

12. A composition as claimed in claim 11, wherein said compatability promoting agent further comprises citric acid.

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13. The composition of claim 11 in the form of a injectable preparation.

14. An injectable, gel-forming delivery vehicle, for sustained release of a therapeutic or  
5 diagnostic agent, comprising, based on the total weight of said vehicle, about 10 to about 60% of at least one pharmaceutically acceptable polyacid, about 5 to about 30% of a pharmaceutically acceptable water-soluble non-ionic polymer, said polyacid and said non-ionic polymer  
10 forming a stable insoluble interpolymer complex in water at acidic pH, about 5% to 50% of water and about 5% to 75% of a pharmaceutically acceptable alcohol which solubilizes said insoluble interpolymer complex.

15. A delivery vehicle as claimed in claim 14, wherein said pharmaceutically acceptable polyacid is selected from the group consisting of polymers of acrylic acid, polymers of methacrylic acid, co-polymers of acrylic acid with an ester of acrylic acid or an ester of methacrylic acid and co-polymers of methacrylic  
20 acid with an ester of acrylic acid or an ester of methacrylic, and said pharmaceutically acceptable water-soluble, non-ionic polymer is selected from the group consisting of polyether glycol, polyvinylpyrrolidone, polyoxyalkylene derivatives of ethylene diamine or  
25 polyoxyalkylene derivatives of propylene glycol.

16. A delivery vehicle as claimed in claim 14, wherein said polyacid comprises polymethacrylic acid of 15,000 average molecular weight and said non-ionic polymer comprises polyethylene glycol of 18,500 average  
30 molecular weight.

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17. A delivery vehicle as claimed in claim 14, further comprising a diagnostically effective amount of a diagnostic agent.

5 18. A delivery vehicle as claimed in claim 14, further comprising a therapeutically effective amount of a therapeutic agent.

10 19. A delivery vehicle as claimed in claim 18, which further includes up to about 50% by weight of a compatability promoting agent which renders said therapeutic agent and said delivery vehicle compatible.

20. A delivery vehicle as claimed in claim 19, wherein said compatability promoting agent comprises glycerin.

15 21. A delivery vehicle as claimed in claim 20, wherein said compatability promoting agent further comprises citric acid.

20 22. A method for sustained delivery of a therapeutic agent to a patient, said method comprising administering to said patient an injectable, gel-forming pharmaceutical composition comprising a therapeutically effective amount of a therapeutic agent and a sustained-release delivery vehicle comprising, based on the weight of said composition, about 4% to about 60% of at least one pharmaceutically acceptable polyacid, about 2 to 25 about 30% of at least one pharmaceutically acceptable water-soluble non-ionic polymer, said polyacid and said non-ionic polymer forming a stable, insoluble interpolymer complex in water at acidic pH, about 5% to 50% of water, about 5% to 75% of a pharmaceutically 30 acceptable alcohol which solubilizes said insoluble interpolymer complex, and up to 50% of a

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pharmaceutically acceptable compatability promoting agent which renders said therapeutic agent and said delivery vehicle compatible.

23. A method as claimed in claim 22, wherein  
5 said pharmaceutically acceptable polyacid is selected from the group consisting of polymers of acrylic acid, polymers of methacrylic acid, co-polymers of acrylic acid with an ester of acrylic acid or an ester of methacrylic acid and co-polymers of methacrylic acid  
10 with an ester of acrylic acid or an ester of methacrylic, and said pharmaceutically acceptable water-soluble, non-ionic polymer is selected from the group consisting of polyether glycol, polyvinylpyrrolidone, polyoxyalkylene derivatives of ethylene diamine or  
15 polyoxyalkylene derivatives of propylene glycol.

24. A method as claimed in claim 22, wherein said composition is administered subcutaneously.

25. A method as claimed in claim 22, wherein said composition is administered intramuscularly.

20 26. A method as claimed in claim 22, wherein said composition is administered intaperitoneally.

27. An injectable, gel-forming sustained release pharmaceutical composition for injection into a body for pharmacological treatment of a condition  
25 requiring such treatment, said composition comprising an effective amount of a drug having activity against said condition and a delivery vehicle for said drug, said vehicle comprising, based on the weight of said composition, about 4 to about 60% of at least one  
30 pharmaceutically acceptable polyacid, about 2 to about 30% of at least one pharmaceutically acceptable, water-

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soluble, non-ionic polymer, said polyacid and said non-ionic polymer forming a stable complex interpolymer in water at acidic pH, about 5% to about 50% of water, about 5% to 75% of ethanol, and up to 50% of a  
5 pharmaceutically acceptable compatability promoting agent which renders said drug and said delivery vehicle compatible.

28. A pharmaceutical composition as claimed in claim 27, wherein said pharmaceutically acceptable  
10 polyacid is selected from the group consisting of polymers of acrylic acid, polymers of methacrylic acid, co-polymers of acrylic acid with an ester of acrylic acid or an ester of methacrylic acid and co-polymers of methacrylic acid with an ester of acrylic acid or an  
15 ester of methacrylic, and said pharmaceutically acceptable water-soluble, non-ionic polymer is selected from the group consisting of polyether glycol, polyvinylpyrrolidone, polyoxyalkylene derivatives of ethylene diamine or polyoxyalkylene derivatives of  
20 propylene glycol.

29. A pharmaceutical composition as claimed in claim 27, wherein said polyacid comprises polymethacrylic acid and said non-ionic polymer comprises polyethylene glycol.

25 30. A pharmaceutical composition as claimed in claim 27, wherein said drug is selected from the group consisting of analgesics, anti-arthritis, anti-asthmatics, anti-coagulants, anti-convulsants, anti-depressants, anti-diabetics, anti-neoplastids, anti-  
30 psychotics, anti-hypertensive agents, muscle relaxants, proteins, peptides, anti-bacterial substances, anti-histamines and decongestants, anti-inflammatories, anti-cholinergics, anti-parasitics, anti-viral compounds,

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carbonic anhydrase inhibitors, chelating agents, immunosuppressive agents, anti-metabolites, amoebacidal compounds, trichomonacidal agents, and combinations of said drugs.

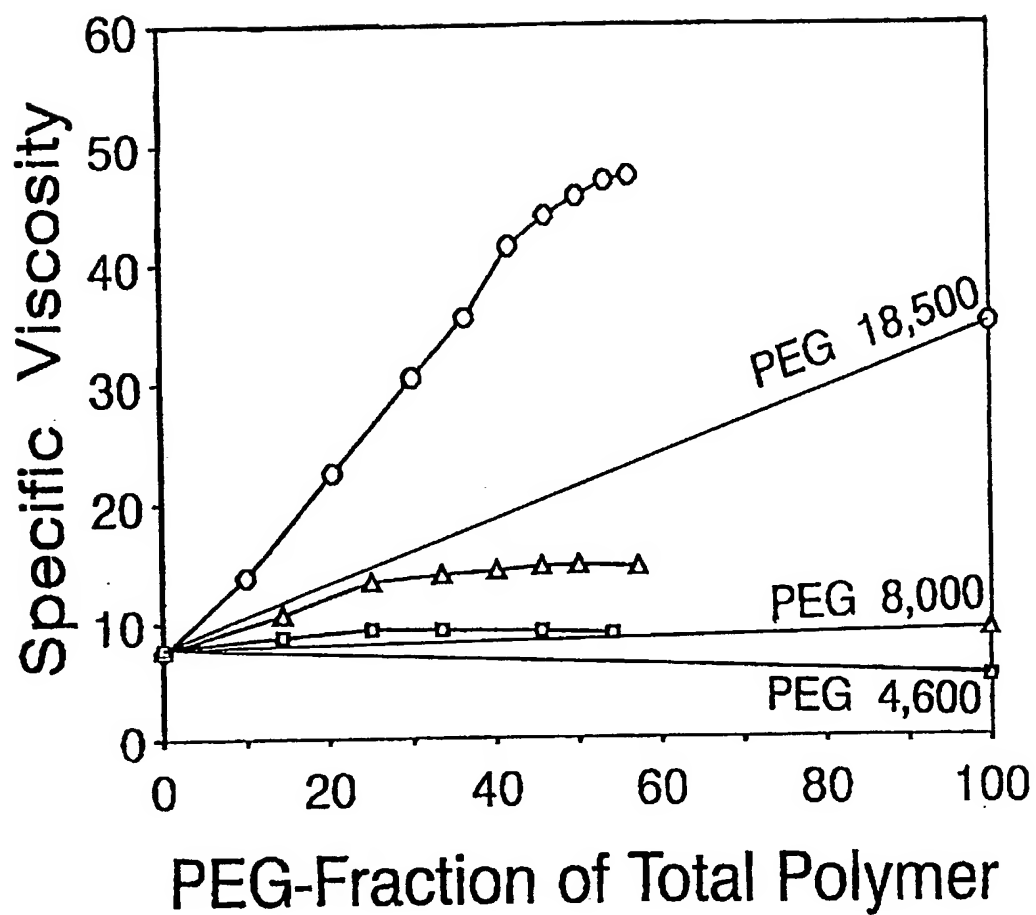


FIGURE 1

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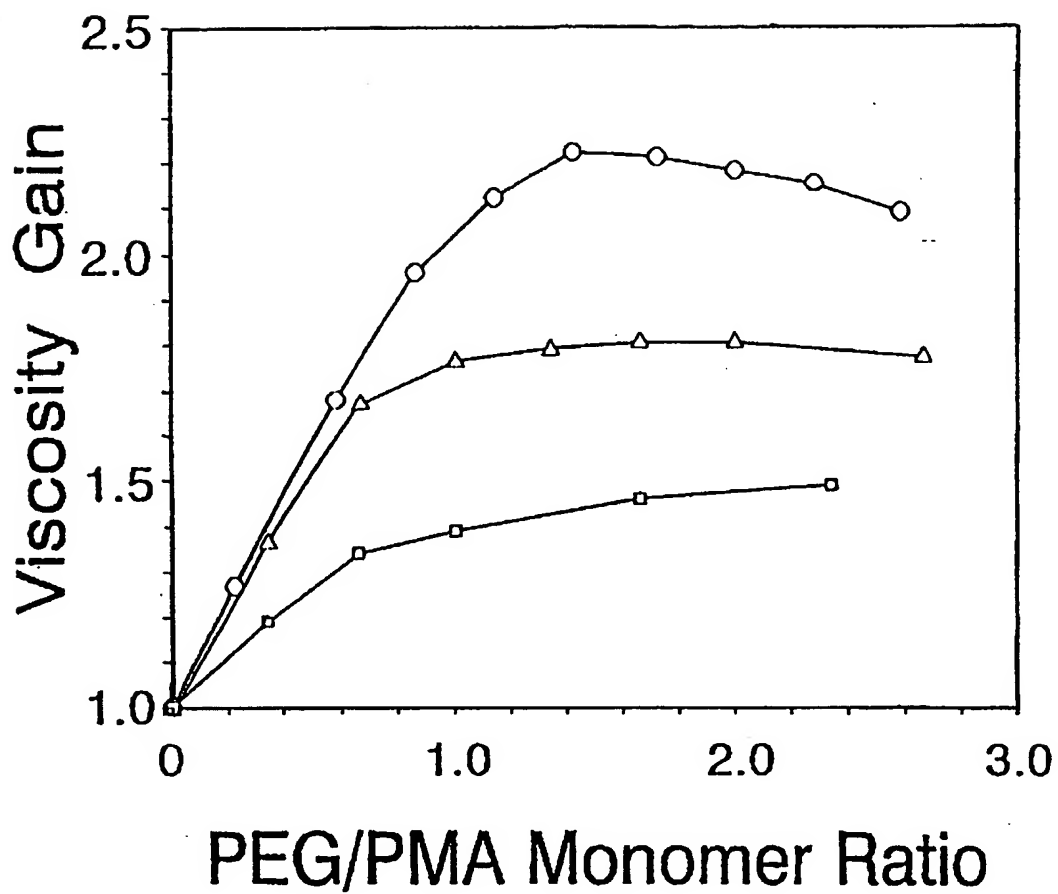


FIGURE 2



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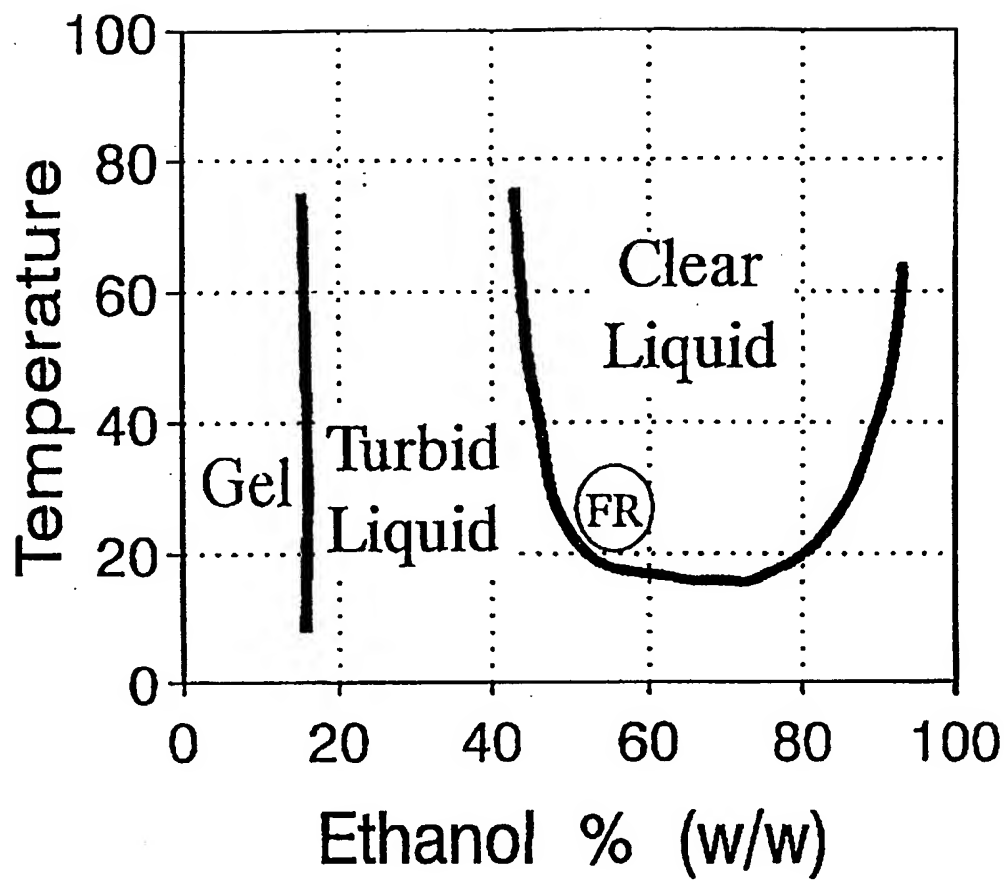


FIGURE 3

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US95/07333

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(6) :A61K 9/10, 47/32, 47/34 US CL :424/486, 487, 484 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 424/486, 487, 484 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Advances in Polymer Science, Volume 41, issued 05 May 1981, E. A. Bekturov et al, "Interpolymer Complexes", pages 99-147, especially page 115.	1-15, 17-28, 30
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document published on or after the international filing date "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family	
Date of the actual completion of the international search 18 JULY 1995		Date of mailing of the international search report 29 AUG 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer <i>D. Freese</i> EDWARD J. WEBMAN Telephone No. (703) 308-2351